Draft Collegium Ramazzini Position paper on Comparative Hazard Assessment (CHA) as a tool for prioritising actions in the control and substitution of hazardous chemicals.

Document trajectory: 1st draft prepared by Vyvyan Howard 26/10/15

2nd draft to be prepared by David Gee

Preamble

The control of chemicals is complex because of the large number that already exist, a list that is being added to by about 1000 new ones each year. Regulation and licensing of chemicals is performed by expert committees appointed by governments using regulatory risk assessment. It is applied to one chemical at a time and is a 'top down' approach. This is both costly and slow, though important. In recent times the reappraisal of chemicals under REACH has commenced but this only addresses high volume products.

We propose the adoption of CHA, to be used in parallel with formal regulatory risk assessment, as a pragmatic approach which can be adopted by producers and consumers as well as by regulators. CHA is simple in principle, universal in applicability and transparent in interpretation. CHA initially requires the collection of toxicological and eco-toxicological data on the set of chemicals under consideration. Some chemical sets are well characterised, pesticides for example, while others will have missing data. A hazard trigger algorithm is then constructed and, for each hazard identified. The aim of the exercise is to be able to assign each chemical to a class which is which is commonly based on a 'traffic light' system. Hazard triggers can be set at multiple levels. In a two level approach chemicals would be assigned to a RED category if the chemical tripped a 1st tier trigger and to an AMBER category if it tripped a 2nd tier trigger. Those chemicals passing through the algorithm without tripping any trigger are assigned to a GREEN category.

Examples of hazard triggers:

Hazard	**RED trigger**	**AMBER trigger**
Mutagenesis	EU Cat 1 & 2	EU Cat 3
Toxicity	WHO Cat 1a	WHO Cat 1b

It should be noted that the setting of particular triggers is completely empirical and can be made to suite the particular concerns/interests of the organisation performing the CHA. Hazard triggers can be set for many different aspects of chemical hazard, including: ADI, Soil persistency and mobility, OSPAR, water persistence, bioaccumulativity, toxicity, carcinogenicity, endocrine disruption, reproductive toxicity, mutagenicity, PIC and occupational health. There are internationally agreed categories/limits for most of these hazards produced by EU, USEPA, IARC, WHO etc. A further refinement can be to assign a numerical score to each hazard trigger level. This can then be used to rank chemicals by their total 'trigger trip' score into a list from the most to the least hazardous. Empirical choices can then be made as to which chemicals will be used or incorporated into

products, based on the scores. The treatment of missing data can take several forms. The ultra precautionary stance would be to assign the chemical to the RED class. However, depending on the perceived seriousness of hazard, it would be assigned some appropriate numerical penalty score. The advantage of treating missing data in this way is that it will put pressure on the producer to perform the work necessary to fill the data gap.

The advantages of CHA are multiple. It allows producers to respond to pressures from their customers to develop a policy to reduce the levels of hazardous chemicals in their products, without having to wait for governmental regulatory bodies to act. They can become 'informed producers'. Customer/purchaser groups can also develop their own CHAs. There is no law stating that you have to buy something just because someone is making it (maybe TTIP is changing that????). Such groups can put pressure on manufacturers by boycotting products that fall into the RED and/or AMBER classes of the CHA. Once the producers understand the settings of the hazard triggers there will be a tendency for them to become a non-regulatory 'standard' which manufacturers will feel obliged to emulate to maintain market share. This will push developments towards substitution with less toxic components, thus pre-empting regulation by governments. The net result is that this will lead to a 'bottom up' approach to overall hazard reduction. Central websites could be developed for the publication of details of the hazard trigger levels for CHAs produced by different groups.

Below is what VH would like you to treat as a strictly confidential Appendix. You will see that it is still at a draft stage. It contains the criteria that we applied to over 858 pesticide active ingredients (in over 6,600 products) when creating the CHA that David alluded to. It resulted in us recommendation to prohibit the use of 132 active ingredients (many of these subsequently banned by regulatory tox – showing the predictive nature of CHA) and to restrict the use of a further 325. As you will see this was a massive work that took several of us 2 years to complete. It would be sad to lose the chance finally publish it through leakage of the information outside this group. Linda Birnbaum has said that she will have a look at it when we have in a submittable state.

In the text:

Proposed prohibited = RED

Proposed restricted = AMBER

Unrestricted = GREEN

Tables 1-3 define the hazard criteria (you will all know these)

Table 4 gives the trigger values adopted for human health

Table 5 gives the trigger values adopted for environmental health

Figure 1: Hazard trigger algorithm flow chart

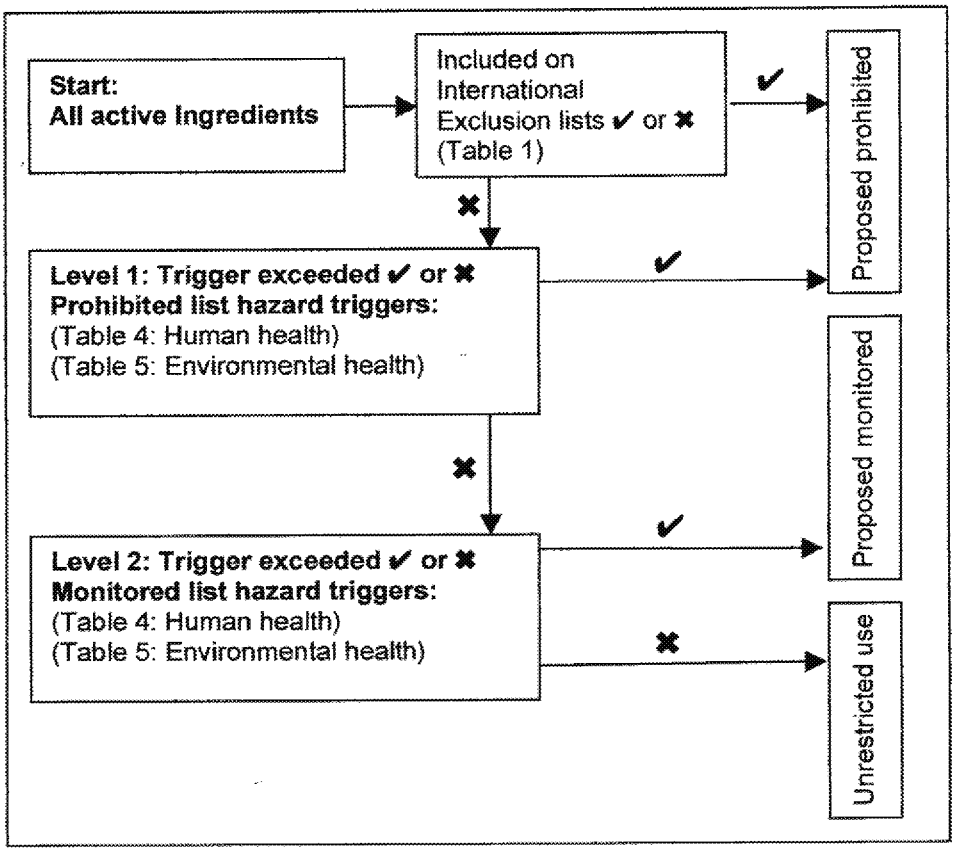

Table 1: Hazard Triggers: Internationally agreed lists

Internationally agreed list	Description
POPs – (Persistent Organic Pollutants)	The Stockholm Convention is a global treaty designed to protect human health and the environment from POPs. POPs are chemicals that remain intact in the environment for long periods, and are toxic to humans and wildlife.
PIC - (Prior Informed Consent)	Pesticides included in the PIC list have been banned or severely restricted by two countries in two regions of the world under criteria in the PIC Rotterdam Convention. Importing countries must indicate whether they allow or prohibit import, exporting countries must ensure compliance. The

	Convention is implemented through EU Regulation 304/2003.
OSPAR (Convention for Protection of Marine Environment in NE Atlantic)	OSPAR guides international co-operation on the protection of the marine environment of the North-East Atlantic. It lists substances that may harm marine environment. There are two lists: Priority List and Possible Concern. OSPAR has established a 'dynamic mechanism for selecting and prioritising hazardous substances'.

Sources: (POPs 2001; PIC 1989; OSPAR 1992)

Tables 2 and 3 describe respectively human and environmental health criteria for each of the chosen parameters. The criteria selected are officially recognized by governmental or intergovernmental bodies as being relevant and comprehensive in regulatory and policy risk assessments. The criteria were chosen to reflect the range of environmental hazards to land, air and water, and of health hazards at work and in the community (an example is provided in Box 1).

Box 1

Occupational Exposure – hazard trigger

For example, in the case of occupational exposure, the triggers have been set using a well accepted standard of exposure – in this case the existence of an Operational Exposure Standard (OES) or Maximum Exposure Level (MEL).
The algorithm places any active ingredient with an MEL set on the Proposed Prohibited List whilst one with an OEL < 1mg/m3 assigns the active ingredient to the Proposed Monitored List since we have used this method, the exposure levels have changed to worker exposure levels but the method still stands.

Table 2: Definition of Hazard Trigger Criteria: Human health

Criterion	**Description**
Chronic – Acceptable Daily Intake (ADI); or in the US Reference Dose (RfD) [mg/kg bw/d]	An ADI is derived from complicated set hazard and exposure assessments. Firstly, a range of toxicology studies allows the determination of the daily dose of a pesticide which can be given over a specified time by a particular dose route, at which no effects are observed. This is known as the No-Observed-Effect Level (NOEL). The No-Observed Adverse-Effect- Level (NOAEL) is the

<table>
<tr><td></td><td>highest dose at which no toxic (ie adverse) effects are observed. Once established, the lowest (or most appropriate or relevant) NOEL or NOAEL is then used to set an ADI [or Reference Dose (RfD) in the US] for humans. This is done by dividing the NOEL or NOAEL by an uncertainty factor, usually 100. The ADI is the amount of a substance which can be ingested every day of an individual's entire lifetime, in the practical certainty, on the basis of all known facts, that no harm will result. Although taken to be synonymous with the ADI, the US RfD has its own definition. The RfD is an estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime. It does not assume that all doses below the RfD are 'acceptable' (or risk free), not that all doses which exceed the RfD are necessarily unacceptable. The RfD is derived from the NOAEL divided by and uncertainty factor and a modifying factor (the latter involving a professional judgement on the entire database of the chemical). (Davies L, O'Connor M, Logan S. 2004: 219-221; ACP 2005).</td></tr>
<tr><td>Acute (LD_{50} mg/kg bw – usually oral rat)</td><td>The LD_{50} value is a statistical estimate of the number of mg of toxicant per kg of bodyweight required to kill 50% of a population of test animals, usually rats (WHO 2005: 2).</td></tr>
<tr><td>WHO Toxicity Class (1a, 1b, II, III)</td><td>WHO classification of acute toxicity is listed below:

<table>
<tr><td>Class</td><td></td><td colspan="4">LD50 for the rat (mg/kg body weight)</td></tr>
<tr><td></td><td></td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td></td><td></td><td>Solids</td><td>Liquids</td><td>Solids</td><td>Liquids</td></tr>
<tr><td>Ia</td><td>Extremely hazardous</td><td>5 or less</td><td>20 or less</td><td>10 or less</td><td>40 or less</td></tr>
<tr><td>Ib</td><td>Highly hazardous</td><td>5 - 50</td><td>20 - 200</td><td>10-100</td><td>40 – 400</td></tr>
<tr><td>II</td><td>Moderately hazardous</td><td>50 - 500</td><td>200 - 2000</td><td>100-1000</td><td>400 – 4000</td></tr>
<tr><td>III</td><td>Slightly hazardous</td><td>Over 500</td><td>Over 2000</td><td>Over 1000</td><td>Over 4000</td></tr>
</table>
Source: WHO 2005: 3.</td></tr>
<tr><td>Endocrine Disruptor (Possible EDs listed)</td><td>Endocrine disrupters are substances that alter the function(s) of the endocrine (hormone) system, and consequently cause adverse effects in organism, progeny or sub-populations (EU 2006). There are a number of lists of suspected EDs from EU, US EPA, German</td></tr>
</table>

	Environment Agency, and World Wide Fund for Nature. There is no definitive protocol to demonstrate ED properties.
Carcinogenic (Various lists from IARC, EU, US EPA)	A carcinogen is a substance capable of increasing malignant tumours; if benign, it may also be considered as carcinogenic. The International Agency for Research on Cancer (IARC), US Environmental Protection Agency and EU have agreed lists or categories which define the likelihood of a substance being carcinogenic.
Reproductive (Cat. 1, 2, or 3)	The European Union has defined categories of pesticides with reproductive concern. Category 1 confers and direct association and categories 2 and 3 acknowledge potential association, where absolute certainty is not known.
Mutagenic (Cat. 1, 2 or 3)	The EU has also developed pesticides of mutagenic concern. (A mutagen is a substance that interacts with and produces changes in DNA). Category 1 confers and direct association and categories 2 and 3 acknowledge potential association, where absolute certainty is not known.
Occupational AOEL – mg/kg bw/d MEL – mg/m^{-3} OES - mg/m^{-3} for 8 hours	The Adverse Occupational Exposure Level (AOEL) (derived in a similar way as the ADI) is defined as a level of daily exposure that would not cause adverse effects in operators who work with a pesticide regularly over a period of days, weeks or months. Depending on the pattern of usage of the pesticide, regulators may consider it appropriate to define a short-term AOEL (i.e. for exposures over several weeks or on a seasonal basis), a long-term AOEL (i.e. for repeated exposures over the course of a year) or both (ACP 2005: 10). Exceeding the Maximum Exposure Limit (MEL) may cause serious health effects (e.g. cancer or asthma) where "safety" cannot be determined, or practicably controlled. The Occupational Exposure Standard (OES) confers no indication of risk to worker health by inhalation day after day (based on current scientific knowledge).

Sources: ACP 2005; Davies L, O'Connor M, Logan S. 2004; EU 2001; German Environment Agency 2001; IARC 2004; PAN UK 2005;US EPA 2004; WHO 2004.

Table 3: Definition of Hazard Trigger Criteria: Environmental health

Criteria	Description
Soil persistence (DT_{50} days)	The half life of a pesticide in soil is measured in time (days) until 50% of the chemical has degraded (measured at 20°C).

Soil mobility (K_{oc} - coefficient)	The potential for a pesticide to be mobile within soils has important implications for contamination of ground water and surface water. leaching into deeper layers of soil is measured by the soil adsorption coefficient (Freundlich's – K), taking account of soil carbon content – K_{oc} (the soil-organic-carbon distribution co-efficient).
Water persistence (DT_{50} days)	The half life of a pesticide in water is measured in the time (days) taken for 50% of the chemical to degrade.
Aquatic toxicity (LC_{50} ug/l)	The LC_{50} represents the concentration at which 50% of test species are killed. The time of exposure is important and must also be stated; eg the 48 Hour LC_{50}.
Bio-accumulation or magnification (K_{ow}) (BCF – bio-concentration factor)	Biomagnification is the total process in which tissue concentrations of a chemical increase through two or more trophic levels. Bioconcentration is a process in which compounds or substances enter organisms directly (eg through gills) and concentrate in tissue. Bioaccumulation includes bioconcentration and also the uptake of residues directly or indirectly through the food chain. The Octanol/water partition coefficient K_{ow} is the ratio of the concentration of a chemical in octanol and in water at equilibrium and at a specified temperature. Octanol is an organic solvent that is used as a surrogate for natural organic matter. This parameter is used in many environmental studies to help determine the fate of chemicals in the environment. An example would be using the coefficient to predict the extent a contaminant will bioaccumulate in fish (USGS 2006). The Bio Concentration Factor (BCF) is the quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure, divided by the concentration in the surrounding water at the same time or during the same period (EIONET 2006).

Source: (USGS 2006; EIONET 2006)

Tables 4 and 5 state the selected trigger levels for each of the lists. These values have been arrived at through debate and consensus of a review group consisting of (see Annex XX). Some trigger values are based upon existing regulatory categories. Tables 4 and 5 should be regarded as 'live documents' which are kept under review and can be modified in the light of new scientific data.

Table 4: Hazard Triggers: Human health

Criterion	Proposed Trigger	
	Prohibit	**Monitor**
Chronic (ADI/RfD mg/kg bw)	<0.0005	NA
Acute (Oral rat - LD50 mg/kg bw) (WHO Toxicity Class)	[Equiv < 5], (WHO Class Ia)	[Equiv < 50], (WHO Class Ib)
Endocrine Disruptor	EU High	EU Low
Carcinogenic	EU 2; EPA A+B1; IARC 2A	EU 3; EPA B2+C+L1+L2; IARC 2B
Reproductive	EU Cat 1+2	EU Cat 3
Mutagenic	EU Cat 1+2	EU Cat 3
Occupational	MEL Set	OES < 1.0mg/m^{-3}

Sources: PAN UK 2005; EU 2004; IARC 2004)

Note: The 'prohibit trigger' heading means the relevant pesticide falls into one of the following categories: 'confirmed', 'probable' or 'may cause' the particular hazard listed. The pesticide under the 'monitor' heading have a lesser 'possible' association with the hazard listed.

Table 5: Hazard Triggers: Environmental health

Criterion	Proposed Trigger	
	Prohibit	**Monitor**
Soil persistence days (DT_{50} for mineralization) – @ 20°C	> 40[1]	> 60[2]
Soil mobility (K_{oc})[3]	<50 'very highly mobile'	50 -150 'highly mobile
Water persistence days – surface (DT_{50})[4]	> 40	30-40
Bio-concentration (BCF[5])	> 5000 'resembles POP'	500 – 5000 'substances hazardous to environment';
Bio-magnification or accumulation log K_{ow} [6]	> 5 'resembles POP'	4-5

[1] PAN (2004) Position on EU Pesticides Authorization April 2004, PAN Europe. Available at http://www.pan-europe.info/publications/010404.shtm

[2] Author's estimate

[3] McCall (1980) Secondary source from Hamilton and Crossley (2003) David Buffin to check and verify from primary.

[4] Author's estimate based on PAN (2004) Position on EU Pesticides Authorization April 2004, PAN Europe. Available at http://www.pan-europe.info/publications/010404.shtm

[5] OSPAR (1992) List of substances of possible concern

[6] OSPAR (1992) op cit Charlie to check on link with CoSSH